REMARKS

The Official Action dated August 4, 2006 and references cited therein have been carefully reviewed. In view of the amendments and evidence submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the prosecution:

The Action noted that trademarks, such as "Duro Tak" and "PVP/VA-S630" used in the specification should be capitalized.

Claims 163-174 are pending and were examined. All claims were rejected on the grounds of nonstatutory double patenting as allegedly unpatentable over claims 1-34 of U.S. Patent 7,045,145.

Claims 163-166 and 171-174 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. 5,762,956 (the 956 patent) in view of U.S. 5,023,084 (the 084 patent).

Claims 167-170 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the 956 patent in view of the 084 patent, and further in view of U.S. 6,007,835 (the 835 patent).

Current amendments to the specification and claims.

The specification has been amended to capitalize "DURO TAK". The term "PVP/VA-S630" was already capitalized, so could not be further altered.

The claims have not been further amended. Applicant submits that the currently pending claims are in condition for allowance, as they are directed to novel and non-obvious subject matter. Support for Applicant's position is set forth below.

The nonstatutory obviousness-type double patenting rejection can be overcome:

The present application and U.S. Patent No. 7,045,145 are commonly owned. A terminal disclaimer in compliance with 37 CFR 1.321(c) or (d) will be filed upon determination of allowable subject matter.

The claimed subject matter is not obvious in view of the cited prior art:

Claims 163-166 and 171-174 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. 5,762,956 (the 956 patent) in view of U.S. 5,023,084 (the 084 patent). Claims 167-170 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the 956 patent in view of the 084 patent, and further in view of U.S. 6,007,835 (the 835 patent). Applicant respectfully traverses these rejections.

When applying 35 U.S.C. § 103, the following tenets of patent law apply: (1) the claimed invention must be considered as a whole; (2) the reference must be considered as a whole and must suggest the desirability and thus the obviousness of making the modification or combination; (3) the reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); MPEP §2141.

These requirements are not met by the cited references, alone or in combination. The claimed system and method call for a *combination* of four skin permeation enhancers. Each of these limitations must be taught or suggested by the cited references. They are not. The 956 patent teaches only a combination of three enhancers. There is nothing in the 956 patent to teach the desirability of adding a fourth enhancer. The 084 patent teaches that capric acid is a skin permeation enhancer, and may be used in transdermal delivery of steroid hormones. However, the 084 patent does not teach the use of capric acid *in combination* with other particular skin permeation enhancers, or even that capric acid would be useful in combination with other enhancers. Moreover, the 084 patent teaches a list of skin permeation enhancers that might be useful to enhance delivery of steroid hormones, but does not teach that combinations of such enhancers could or should be used instead of single enhancers. Thus, taken as a whole, the cited references provide no motivation, in and of themselves, for combination to arrive at the invention as presently claimed.

Even assuming, *arguendo*, that the 956 patent and the 084 patent suggested the addition of capric acid to the 956 patent's enhancer combination, the suggestion would be merely to try the additional ingredient – there is no teaching that would impart to the skilled artisan any reasonable expectation that such a modification would be successful.

The addition of the 835 patent to support the rejection of claims 167-170 is also untenable in view of the absence of teaching in the 956 patent and the 084 patent of the invention as currently claimed. The 835 patent's purported teaching of PVP/VA-S30 do not supply the suggestion or motivation to combine the cited references so notably absent from the primary references.

Since the cited references do not provide any teaching or motivation to combine them to arrive at the invention as claimed, that motivation must have come from Applicant's disclosure, and not from the cited references themselves. Such use of Applicant's disclosure to glean the motivation to modify prior art teachings constitutes hindsight reasoning of a type that is impermissible to support an obviousness rejection. MPEP §2145.

For each of the reasons set forth above, the presently claimed invention cannot be said to be obvious in view of the cited references. The rejections under 35 U.S.C. §103(a) should therefore be withdrawn for these reasons alone. However, to advance the claims to allowance, and without intending to acquiesce to the correctness of the examiner's position, Applicant submits herewith additional evidence of non-obviousness, by way of (1) the Declaration of Agis Kydonieus, Ph.D., and (2) the Declaration of Thomas M. Rossi, Ph.D.

Paragraphs 2-5 of Dr. Kydonieus' Declaration set forth his qualifications as one of deep experience and skill in the art of transdermal drug delivery. In his Declaration, Dr. Kydonieus sets forth a detailed explanation as to why the transdermal system claimed the present application is not obvious in view of the cited references. First, as detailed in Paragraphs 9-17, the field of transdermal drug delivery is not predictable. Dr. Kydonieus sets forth a detailed explanation as to why this is the case, even when enhancers are not used (Kydonieus Decl. ¶¶10-13). When chemical enhancers are employed, the complexity and unpredictability of transdermal systems increase because they behave substantially differently when co-delivered with other enhancers and with the drugs themselves (Kydonieus Decl. ¶¶14-16). For these reasons, the effect of enhancers on the permeation of drugs through skin is unpredictable and dependent on many variables whose effect can only be determined by experimentation (Kydonieus Decl., ¶17).

Second, as detailed in Paragraphs 18-20, Dr. Kydonieus believes that the unpredictability in the art would have made it impossible for the skilled artisan to arrive at the presently claimed formulation from the information provided in the 956 and 084 patents. Dr.

Kydonieus points out that the system of the 956 patent was deficient in part because of insufficient delivery of progestin hormone to the bloodstream, and that the present invention overcomes this deficiency by making a modification to the enhancer system, namely, by adding a small amount of capric acid (Kydonieus Decl., ¶18). Dr. Kydonieus explains in detail why the 084 patent's information was completely insufficient to provide the skilled artisan with any guidance as to how to improve on the system of the 956 patent in the manner claimed in the present application (Kydonieus Decl., ¶19). He concludes that the presently claimed specific modifications of the 956 patent's system could not have been imparted in any way to the skilled artisan by the teachings of the 084 patent, and that significant trial-and-error experimentation was likely the means by which the inventor settled upon the claimed modifications (Kydonieus Decl., ¶20).

The explanations and opinions of Dr. Kydonieus as summarized above should provide a more than sufficient basis for reconsideration and withdrawal of the rejections under 35 U.S.C. §103, inasmuch as they clearly support the argument that a *prima facie* case of obviousness has not been established, based on the cited references. However, the Declaration of Dr. Kydonieus goes on to provide a further rationale for such action. Namely, as detailed in Paragraphs 21 and 22, Dr. Kydonieus notes the comparative *in vitro* and *in vivo* data presented by the 956 patent and the present application and its parent (Kydonieus Decl., ¶21). He points out that the *in vitro* skin flux results with the capric-acid containing patch of the present invention were actually poorer than that of the 956 patent's transdermal system, yet in the clinical studies, the steady state serum concentration of progestin delivered by the present invention's system was several-fold better than that delivered by the same size patch of the 956 patent's system (Kydonieus Decl., ¶22). Dr. Kydonieus is of the opinion that this many-fold improvement in *in vivo* progestin delivery by re-formulating the matrix to include capric acid was not expected, and could not have been predicted from the information presented in the 956 patent or the 084 patent.

The Declaration of Thomas R. Rossi sets forth yet additional evidence of non-obviousness of the present invention, specifically, evidence of commercial success. Dr. Rossi currently serves as President and Chief Executive Office of Agile Therapeutics, Inc., licensee and developer of the technology disclosed and claimed in the present application (Rossi Decl., ¶6). Dr. Rossi also notes the excellent *in vivo* results afforded by a transdermal

delivery system of the present invention, as compared with that of the 956 patent, and that such results could not have been predicted from the information taught in the cited references (Rossi Decl., ¶8). Dr. Rossi attests that the robust delivery of progestin afforded by the system of the present invention, but lacking in the 956 patent's system, was the impetus for Agile Therapeutics to license the technology and to invest in development of a commercial product (Rossi Decl., ¶9). Dr. Rossi elaborates that Agile Therapeutics and its predecessor have raised a total of $31.5 million dedicated to product development activities based on the invention of the present application. He notes that these investments were made by high quality private equity investors with experience in health care product development and commercialization (Rossi Decl., ¶10). Clearly, the commercial success of the technology covered by the claimed invention, as attested to by Dr. Rossi in his Declaration, must be taken as further compelling evidence of the non-obviousness of the present invention over the cited prior art.

In summary, Applicant has presented reasoning and evidence to support his assertion that a *prima facie* case of obviousness based on the cited references has not been established because, in view of the general unpredictability of transdermal drug delivery, one seeking to improve on the transdermal system of the 956 patent would not have found sufficient information in any of the cited references, alone or in combination, to make the specific modifications claimed in the present application. Furthermore, though not believed to be necessary, through the Declarations of Dr. Kydonieus and Dr. Rossi, Applicant has highlighted comparative data within the specifications of the 956 patent and the present application and its parent, demonstrating unexpectedly good *in* vivo results achieved through the presently claimed formulations. Finally, though again not believed to be necessary, Applicant has set forth an additional indication of non-obviousness, namely, commercial success of the presently claimed transdermal system, as attested to in the Declaration of Dr. Thomas Rossi. For each of the foregoing reasons, the presently claimed invention cannot be said to be obvious in view of the cited references. Applicant therefore requests reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

Conclusion:

In view of the foregoing remarks and the evidence submitted herewith, the presently-pending claims are believed to be in condition for allowance. Applicant respectfully requests early and favorable reconsideration and withdrawal of the rejections set forth in the August 4, 2006 Official Action, and allowance of this application.

Respectfully submitted,

Date: November 6, 2006

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